Kinetic Uncertainty Relations for the Control of Stochastic Reaction Networks

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Nonequilibrium stochastic reaction networks are commonly found in both biological and nonbiological systems, but have remained hard to analyze because small differences in rate functions or topology can change the dynamics drastically. Here, we conjecture exact quantitative inequalities that relate the extent of fluctuations in connected components, for various network topologies. Specifically, we find that regardless of how two components affect each other's production rates, it is impossible to suppress fluctuations below the uncontrolled equivalents for both components: one must increase its fluctuations for the other to be suppressed. For systems in which components control each other in ringlike structures, it appears that fluctuations can only be suppressed in one component if all other components instead increase fluctuations, compared to the case without control. Even the general N-component system—with arbitrary connections and parameters—must have at least one component with increased fluctuations to reduce fluctuations in others. In connected reaction networks it thus appears impossible to reduce the statistical uncertainty in all components, regardless of the control mechanisms or energy dissipation.

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From biochemistry to ecology, biological systems can form stochastic interaction networks where components present in low numbers affect each other's production or degradation rates. Predicting the dynamical heterogeneity this creates is exceedingly difficult, both because most nonlinear systems are analytically unsolvable and because even the simplest networks, including those with just two components, can display oscillations, multimodality, bursting, noise suppression, and a range of other features depending on exact parameters and connections, which often are unknown [1–4]. However, some general rules apply regardless of parameters and the form of rate functions [5–12]. For example, for deterministic dynamical systems, Bendixson's criterion states that there are broad classes of feedback systems that cannot display stable limit cycles [5]. Here, we consider similar types of systems but at the level of stochastic birth and death events rather than deterministic continuous changes, and look for constraints on the pattern of fluctuations that can arise.

We first ask whether feedback loops between two components can reduce spontaneous fluctuations in both of them, compared to systems with the same average abundances but constant rates. That is, we consider if there exist rate functions such that the noise suppression can be mutual, or if one component must display significant fluctuations in order for other components to have reduced fluctuations. Specifically, we consider the case where components X_1 and X_2 are present in integer numbers and change in probabilistic birth and death events:

$$x_1 \xrightarrow{f(x_2)} x_1 + b_1, \qquad x_1 \xrightarrow{x_1/\tau_1} x_1 - 1,$$
$$x_2 \xrightarrow{g(x_1)} x_2 + b_2, \qquad x_2 \xrightarrow{x_2/\tau_2} x_2 - 1. \tag{1}$$

All rates are propensities, i.e., continuous-time transition probabilities for jumps between the integer-valued states. The τ are average lifetimes and b_1 and b_2 are integer birth sizes that often equal one but could be large and randomly distributed, e.g., when components are produced in bursts or litters [13–16]. The reaction rates $f(x_2)$, $g(x_1)$ are allowed to take any functional form; i.e., the components can arbitrarily affect each other's production rates. This includes oscillatory or multimodal behavior, and we only exclude systems that cannot become statistically stationary, e.g., due to infinite lifetimes or absorption at state $\{x_1, x_2\} = \{0, 0\}$ if $f(0) = g(0) = 0$. We consider more complex reaction topologies below, but many systems selected to suppress noise create minimal feedback loops to reduce information losses from stochastic signaling events, and models of such systems have often been similar to special cases of Eq. (1) [17,18].

Effective noise suppression generally requires fast feedback responses, such that the system can self-correct existing perturbations before new ones arise. Though the

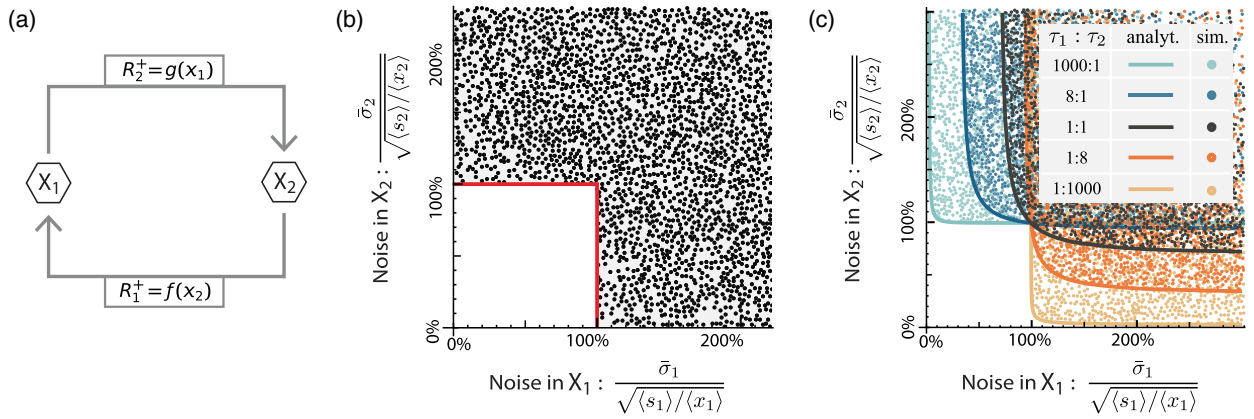

FIG. 1. Trade-off for mutual control systems. (a) We consider the following generic class of mutual control systems: each component is assumed to decay with some (unspecified) half-life but the way in which the two components affect each other's production rates R_i^+ is left completely unspecified, see Eq. (1). (b) Analytical results suggest that no such control system can simultaneously suppress noise in both components below their respective Poisson fluctuations (denoted by 100% in the diagram). We find numerically that the bounds derived in the high copy number regime (red lines) in fact constrain all tested systems (black dots) regardless of noise levels and copy numbers. This numerical confirmation suggests that no mutual control system—regardless of chosen control functions or parameters—can simultaneously exhibit sub-Poisson fluctuations in both components as indicated by the lack of data points in the lower left. (c) Here, we present the analytical bounds (colored lines) of Eq. (4) for different lifetimes together with exact numerical realizations of systems with nonlinear control systems (dots). The colors correspond to fixed relative lifetimes, and each dot corresponds to a different system with a different set of control functions and parameters [see Supplemental Material (SM) for numerical details [19]]. For each ratio of relative lifetimes none of the tested systems beat the limit of Eq. (4).

average lifetimes of the two components cannot both be short relative to each other, the nonlinear rate functions could amplify even small changes in one component into large changes in the production rate of the other [7] and thus in some sense respond quickly to changes. Despite that, we here conjecture that no such systems, regardless of parameters and rate functions $f(x_2)$ and $g(x_1)$, could reduce stationary fluctuations in both components, compared to the corresponding open-loop system where f and g are constant, for the same averages and burst statistics. In the absence of bursts ($b_i = 1$) this means that X_1 and X_2 cannot both display sub-Poisson fluctuations, which we refer to as an inaccessible Poisson square (Fig. 1).

We first consider the stationary small noise limit at high copy numbers [20,29] where the normalized covariance matrix with elements $\Sigma_{ij} = \mathrm{Cov}(x_i, x_j)/(\langle x_i\rangle\langle x_j\rangle)$ satisfies the Lyapunov equation

$$A\Sigma + \Sigma A^T + D = 0. \tag{2}$$

Here, A is the Jacobian matrix for the dynamics of the average abundances (normalized by their steady states) subject to small deviations, and D is the system's diffusion matrix. For the class of systems defined in Eq. (1), $A_{ii} = -1/\tau_i$ while the off-diagonal entries are unknown parameters that depend on the unspecified control functions. Because here each reaction only changes one component, the diffusion matrix is diagonal with entries (see SM [19]):

$$D_{ii} = \frac{2}{\tau_i}\frac{\langle s_i\rangle}{\langle x_i\rangle}, \tag{3}$$

where $\langle s_i\rangle = (\langle b_i\rangle + 1)/2$ is the average jump size for component X_i. Solving Eq. (2) for the normalized standard deviations $\bar{\sigma}_i := \sqrt{\Sigma_{ii}}$, which we will colloquially refer to as "noise" throughout this Letter, in terms of the unknown covariance Σ_{12} gives

$$\tau_1\bar{\sigma}_1^2\left(\bar{\sigma}_2^2 - \frac{\langle s_2\rangle}{\langle x_2\rangle}\right) + \tau_2\bar{\sigma}_2^2\left(\bar{\sigma}_1^2 - \frac{\langle s_1\rangle}{\langle x_1\rangle}\right) = (\tau_1+\tau_2)\Sigma_{12}^2. \tag{4}$$

Because the right hand side of Eq. (4) cannot be negative we must have

$$\bar{\sigma}_i \geq \sqrt{\langle s_i\rangle/\langle x_i\rangle} \text{ for at least one } i, \tag{5}$$

where $\sqrt{\langle s_i\rangle/\langle x_i\rangle}$ corresponds to the noise without control, i.e., for constant rates. Thus, no such system could suppress noise in both components below their uncontrolled levels.

For any finite ratio of lifetimes, the small-noise approach further predicts that the normalized standard deviation in X_1 cannot be lower than a factor $\sqrt{1+\tau_1/\tau_2}$ below the noise when the rates are constant, and vice versa for X_2. In fact, when one component is arbitrarily short lived, so that there can be no limit on noise suppression in the other component, the fast component equilibrates to conditional Poisson distributions for each value of the slow component, even for nonlinear functions f and g. The law of total variance—without small-noise approximations—then states (see SM [19]) that Eq. (5) must again hold. Thus, the conjecture holds asymptotically both in the high abundance limits regardless of timescales and for separated timescales regardless of abundances. For intermediate and

low abundances without timescale separation, the exact analytic methods previously developed to identify bounds on stochastic reaction systems [6,7,9] were not helpful for this system. We therefore performed systematic numerical explorations.

First, we used the exact Gillespie algorithm [21] to realize the system in Eq. (1), using a wide range of functions $f(x_2)$, $g(x_1)$, and parameters τ_i, including combinations of sharp and damped functions, ratios of polynomials, exponential functions, etc. (see SM [19]). For all ratios of lifetimes τ_1/τ_2, some systems could get extremely close to the bounds in Eq. (4) but we found none that violate them, suggesting that the inequality is tight and a real physical limit on the system for all nonlinear functions [see Fig. 1(c)]. However, it is only possible to sample a subset of possible functions $f(x_2)$ and $g(x_1)$, as these lie on an infinite-dimensional Hilbert space. We therefore also systematically explored systems in the low copy number regime with less than five or less than ten copies of each type, i.e., with only five or ten values of $f(x_2)$ and $g(x_1)$, respectively. This allows us to more densely sample the space of possible functions (see SM [19]). We considered 10^6 reaction systems of each type, using many different types of functions, including nonmonotonic ones and randomly generated values. Again, many examples get exceedingly close to the predicted bound but none break it. Though short of an exact and general proof, this combination of analytical limits and systematic numerical explorations supports the conjecture of a hard trade-off for all systems in which two components directly control each other. Nonstationary systems can of course start inside the Poisson square, but that would only reflect the choice of initial conditions, not an ability to suppress noise. The physically more relevant question is whether a system moving from one stationary state to another—due to some change in parameters or rate functions—could temporarily move through the Poisson square. This is indeed possible for some special types of systems, but we could only find very minor violations through the upper right corner of the Poisson square (see SM [19]), potentially suggesting bounds even on nonstationary dynamics.

Next, we investigate if these principles generalize to multicomponent systems. First, we consider feedback loops in which the components control each other in a ringlike structure [Fig. 2(a)] where the reactions of component X_i for $i = 2, \ldots, N$ are given by

$$x_i \xrightarrow{r_i(x_{i-1})} x_i + b_i, \qquad x_i \xrightarrow{x_i/\tau_i} x_i - 1, \tag{6}$$

and X_1 has production rate $r_1(x_N)$ and decay rate x_1/τ_1. This describes systems in which feedback acts indirectly, through a cascade of reactions. The same combination of approaches as above suggests that in any N-component feedback ring structure as defined in Eq. (6), only a single component can exhibit fluctuations below Poisson noise

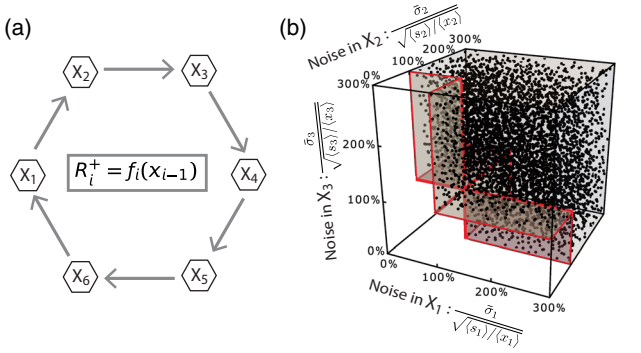

FIG. 2. Trade-offs between pairs of components within a feedback ring. Two-component mutual control systems can be generalized to a multicomponent control feedback loop in which N components affect the production rate of the next component within a ring as defined by Eq. (6). (a) Schematic illustration of a ringlike connection feedback loop for $N = 6$. (b) Numerical support that feedback rings can only suppress noise in at most one component. Considering stochastic realizations of control systems within the class defined by Eq. (6) for $N = 3$ we find numerically that the bounds derived in the high copy number regime constrained all systems regardless of noise levels and copy numbers. Each dot corresponds to the numerical data for a given system with a specified set of control functions and parameters (see SM for numerical details [19]). We find numerical confirmation that no three-component feedback ring can suppress fluctuations in more than one component. Note, that lower-dimensional feedback loops are special cases of the higher-dimensional ones in which some components are infinitely fast with $\tau_i \to 0$. (See Movie S1 in the SM [19].)

[Fig. 2(b)], and that any pair of components X_i, X_j are constrained by

$$\frac{1}{\tau_i}\left(\frac{\bar{\sigma}_i}{\sqrt{\langle s_i\rangle/\langle x_i\rangle}}\right)^{-2} + \frac{1}{\tau_j}\left(\frac{\bar{\sigma}_j}{\sqrt{\langle s_j\rangle/\langle x_j\rangle}}\right)^{-2} \leq \frac{1}{\tau_i} + \frac{1}{\tau_j}. \tag{7}$$

For $N = 3$ this follows from the Lyapunov approach above Eq. (2) in the high copy number limit. The corresponding A matrix then has the following structure:

$$A = \begin{bmatrix} -1/\tau_1 & 0 & A_{13} \\ A_{21} & -1/\tau_2 & 0 \\ 0 & A_{32} & -1/\tau_3 \end{bmatrix}, \tag{8}$$

where A_{12}, A_{32}, and A_{13} again depend on the unspecified control functions. For stability, all eigenvalues of A should have negative real parts, in which case a unique positive definite solution of Eq. (2) exists [22]. Solving Eq. (2) is then inconclusive with respect to showing Eq. (7), since the stability criterion cannot be directly applied. Therefore, instead of solving Eq. (2) for all (co)variances, we looked for a symmetric matrix ψ satisfying the following two conditions:

$$\mathrm{tr}[\psi(A\Sigma + \Sigma A^T)] = A_{11} + A_{22}, \tag{9}$$

$$\psi_{11} \geq 1/\Sigma_{11}, \qquad \psi_{22} \geq 1/\Sigma_{22}, \qquad \psi_{33} \geq 0. \tag{10}$$

If such a ψ exists, the bound Eq. (7) can be shown to follow for $i, j = 1, 2$, and by symmetry the same inequality would exist for all $i \neq j$. For matrices with the structure of Eq. (8) we can show that such ψ indeed exists uniquely (see SM [19]). Then left multiplying by ψ in Eq. (2) and taking the trace—with the same diagonal diffusion matrix D as in Eq. (3)—we have Eq. (7) for $i, j = 1, 2$. However, this approach does not work for $N \geq 4$ since ψ then is not uniquely determined, but for such higher N the conclusion is still supported by a similar systematic numerical approach as above. All components except one would then become sacrificial components to reduce noise in a chosen one.

Next, we consider systems in which N components control each other's production rates in arbitrary topologies as illustrated in Fig. 3(a) and defined by

$$x_i \xrightarrow{r_i(\{x_j : j \neq i\})} x_i + b_i, \qquad x_i \xrightarrow{x_i/\tau_i} x_i - 1. \tag{11}$$

The production rate of each component is allowed to be an arbitrary function of all other components and the degradation of component number i is assumed to be a first-order reaction with a half-life τ_i as above. Because it is rare that components *directly* affect their own production rates, as opposed to using chemical intermediates, this should apply to a large number of systems. We then combine the trace

$$\mathrm{tr}[\Sigma^{-1}(A\Sigma + \Sigma A^T + D)] = 0 \tag{12}$$

with the general constraint that Σ must always be positive semidefinite so $(\Sigma^{-1})_{ii} \geq 1/\Sigma_{ii}$ (see SM [19]). Then since $\mathrm{tr}[\Sigma^{-1}D] = \sum_i D_{ii}(\Sigma^{-1})_{ii} \geq \sum_i D_{ii}/\Sigma_{ii}$, we obtain

$$\sum_{i=1}^{N} \frac{1}{\tau_i} \left(\frac{\bar{\sigma}_i}{\sqrt{\langle s_i \rangle / \langle x_i \rangle}} \right)^{-2} \leq \sum_{i=1}^{N} \frac{1}{\tau_i}. \tag{13}$$

This result for the high copy number limit, which again is supported by systematic numerical explorations at low copy numbers, generalizes the Poisson square into an N-dimensional Poisson hypercube, meaning that at least one component must display larger fluctuations than Poisson in the absence of control [Fig. 3(b)]. While the general feedback topology can improve noise suppression compared to rings, it thus seems impossible to suppress noise in all components, regardless of topology. As above, the result also generalizes to production in distributed bursts.

Similar results appear to apply more broadly. For the arbitrary case in which any component can affect the production or degradation rates of all components including their own

$$x_i \xrightarrow{r_i^+(x_1,\ldots,x_N)} x_i + b_i, \qquad x_i \xrightarrow{r_i^-(x_1,\ldots,x_N)} x_i - 1. \tag{14}$$

we find [19] that

$$\sum_{i=1}^{N} \frac{1}{\tau_i} \left(\frac{\bar{\sigma}_i}{\sqrt{\langle s_i \rangle / \langle x_i \rangle}} \right)^{-2} \leq \sum_{i=1}^{N} \frac{H_i}{\tau_i}, \tag{15}$$

where $H_i = \partial \ln(r_i^-/r_i^+)/\partial \ln(x_i)$ are constants that describe how component X_i controls its own production or degradation rates directly [20]. For example, if one component is produced with rate $\sim x_i^m$ and degraded with rate $\sim x_i^n$, then $H_i = n - m$. For all systems in which the linearized system is stable, the stability criterion implies that the right hand side in Eq. (15) is positive. Thus, for any given level of self-control in such systems, there is again a limit on the noise suppression that can be achieved for all components. To our knowledge, the most common reasons for $H \neq 1$ is self-replication or autocatalysis, where the production rate increases with x and the corresponding H value therefore is closer to zero, or saturated enzymatic degradation, where the death rate per molecule decreases with x and the H value again is closer to zero. Those mechanisms make it even harder to suppress noise. For

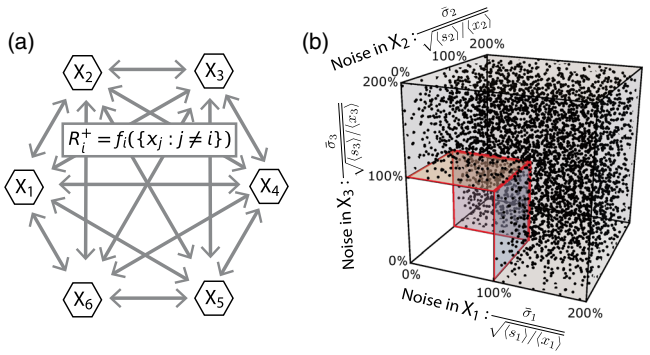

FIG. 3. Trade-off in N-component control networks. Here, we consider N-component control structures of arbitrary topology where each component is allowed to affect any other component's production rate (but not its own) as defined in Eq. (11). (a) Schematic illustration of a maximally connected control network for $N = 6$. Since we leave all reaction rates unspecified (here and throughout the Letter) any specific realization of this class may have rates that depend on only a subset of the other components and may thus be much more sparsely connected than the above illustration—in particular, the ringlike feedback systems of Fig. 2 are a subset of the more general class considered here. (b) Here, we present numerical support for the constraint of Eq. (13) in the $N = 3$ case. We generated an extensive set of numerical realizations of arbitrarily nonlinear three-component feedback systems with arbitrary lifetimes and abundances. Again, we could not find any system that violated the bound derived in the high copy number limit, and conclude that the "Poisson cube" is inaccessible by any three component feedback systems.

autodimerization, where two monomers form a dimer and the degradation rate is approximately proportional to x^2, the H can double from 1 to 2. However, even this mechanism would only marginally reduce the noise, both because the change in H is moderate and because two molecules are now eliminated in the same reaction, which increases the diffusion terms in D. Thus, we believe the principle that chemical reaction networks require some components to fluctuate significantly applies quite broadly.

So far we assumed that each reaction changes abundances in integer steps, and only for one component at a time, as, e.g., transcription or translation events change either the number of messenger RNA or protein, respectively, but not both simultaneously. However, similar results can be derived for reaction systems where the reactions change more than one kind of component, such as systems with complex formation or conversion reactions. The diffusion matrix D then has nonzero off-diagonal entries and the relation $\mathrm{tr}[\Sigma^{-1}D] = \sum_i D_{ii}(\Sigma^{-1})_{ii}$ behind Eq. (13) no longer holds. However, for stable systems where all $H_i > 0$, the relative noise suppression compared to the noninteracting system is still bounded by the quadrant of a hypersphere:

$$\sum_{i=1}^{N} \left(\frac{\bar{\sigma}_i}{\sqrt{\langle s_i \rangle / (H_i \langle x_i \rangle)}} \right)^2 \geq 1, \tag{16}$$

where $\sqrt{\langle s_i \rangle / (H_i \langle x_i \rangle)}$ is the noise of the noninteracting system. For example, adding a coproduction event to our initial example for X_1 and X_2 in Eq. (1), e.g., $\{x_1, x_2\} \to \{x_1 + 1, x_2 + 1\}$, would shrink the inaccessible region from the Poisson square of Eq. (15) into a quadrant of a circle with unit radius (see SM for details [19]). An intuitive reason is that when feedback acts via a low-copy component, intrinsic noise in that component makes control less reliable. With stoichiometrically coupled production reactions, such signaling noise is reduced, but only to some extent.

Summary.—Recent studies have identified many important constraints on the behavior of stochastic systems in terms of energy-related properties, such as entropy production, etc., [8–10,30–33]. However, many processes in biology are so strongly driven that energetic constraints cannot easily be invoked. For example, protein degradation is not protein synthesis in reverse, but a separate energy-consuming process. Those processes can still be subject to other types of constraints though [6,34], e.g., determined by the topology of the reaction network or individual reaction steps that cause a loss of information transfer. Indeed, when we apply our approach to systems that are close to thermodynamic equilibrium we identify very severe bounds (see SM for details [19]), but regardless of energy dissipation we also demonstrate broad trade-offs between fluctuations in different components of stochastic reaction networks, set only by network topology. Specifically we find that molecular networks may require "sacrificial" components with large noise to ensure that others function precisely, which in turn may help explain why cells have so many dedicated control molecules and why so many of them appear to fluctuate substantially [17]. Our systematic numerical explorations further suggest that the analytical asymptotic limits identify bounds that are both exact and tight for all parameters and rate functions. Together with the observation that numerous such bounds exist for different topologies, this may suggest the existence of more general rules for stochastic reaction networks far from equilibrium, which perhaps could be collectively captured by a different perspective from what we can provide.

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